UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/727,658	12/05/2003	Istvan Szelenyi	081117-0127	8943

41552 7590 09/12/2008

MCDERMOTT, WILL & EMERY
4370 LA JOLLA VILLAGE DRIVE, SUITE 700
SAN DIEGO, CA 92122

EXAMINER	
KWON, BRIAN YONG S	

ART UNIT	PAPER NUMBER
1614	

MAIL DATE	DELIVERY MODE
09/12/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/727,658	SZELENYI ET AL.	
	Examiner	Art Unit	
	Brian-Yong S. Kwon	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 July 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *13-30* is/are pending in the application.

4a) Of the above claim(s) *17-24* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *13-16 and 25-30* is/are rejected.

7)☐ Claim(s) *13-16 and 28-30* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *07/11/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Acknowledgement is made of applicants' filing of the instant application as a Request for Continued Examination (RCE) under 37 CFR 1.1114. Claims 13-30 are pending in the application, but claims 17-24 are withdrawn from consideration as being drawn to non-elected invention. Accordingly, claims 13-16 and 25-30 are currently pending for prosecution on the merits.

Claim Objections

2. Claims 13-16 and 28-30 are objected to because of the following informalities: Improper Markush-Type language is utilized.

With respect to claim 13, the members of the Markush group (e.g., tolperisone, eperisone, silperisone, riluzole, propafenone, lidocaine, flecainide and metixen") should be recited in proper Markush-type language, "selected from the group consisting of…and…". Suggest rewording of "selected from the group consisting of tolperisone, eperisone, silperisone, and other tolperisone analogs, and riluzole, propafenone, lidociane, flecainide and metixen, and their pharmaceutically utilizable salts" to "selected from the group consisting of tolperisone, eperisone, silperisone…flecainide and metixen, or their pharmaceutically utilizable salts".

With respect to claims 14-16 and 28-30, for example, suggest rewording of "selected from tolperisone, eperisone, silperisone, and other tolperisone analogs, and pharmaceutically utilizable salts thereof" in claim 14 to "selected from the group consisting of tolperisone, eperisone, silperisone, and other tolperisone analogs, or pharmaceutically utilizable salts thereof". Applicant is also requested to amend claims 28-30 to recite the members of the Markush group in proper Markush-type language.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 13, 14 and 25-28 are rejected under 35 USC 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification discloses that the mechanism of inhibiting Na+ channels could contribute to reducing muscle tone and produce the pain-alleviating effect. The specification discloses namely tolperisone, eperisone, silperisone, riluzole, propafenone, lidocaine, flecainide and metixen as a suitable example of a sodium channel-inhibiting substance, which meet the written description and enablement provisions of 35 USC 112, first paragraph. However, the claims 13, 14 and 25-28 are directed to encompass "a sodium channel-inhibiting or -influencing substance" such as antagonists or partial antagonists of sodium channel, agonist or partial agonists, or mixed antagonist/agonist including sodium/hydrogen exchangers, sodium-glucose transporters, sodium/myoinositol cotransporter, Na+/I- symporter, sodium/potassium/calcium exchanger, Na+/K+/CI- cotrasporter and etc... or "other tolperisone analogs" which only correspond in some undefined way to specifically instantly disclosed chemicals. None of these meet the written description provision of 35 USC 112, first paragraph, due to lacking chemical structural information for what they are and chemical structures are highly variant and

encompasses a myriad of possibilities. To the extent that no structure function data is disclosed in connection with theses functionally described compounds to correlate, or there is not disclosed correlation established between these functional drugs and the contemplated desired therapeutic effect to be achieved in practicing the instant invention, the specification provides insufficient written description to support the genus encompassed by the claims.

Vas-Cath Inc. Mahurkar, 19 USPQ2d 1111, makes clear the "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116).

With the exception of tolperisone, eperisone, silperisone, riluzole, propafenone, lidocaine, flecainide and metixen, the skilled artisan cannot envision the detailed chemical structure of the encompassed derivatives, analogs, etc., regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai pharmaceutical Co. Ltd., 18 USPQ2d 1016. In Fiddes v. Baird, 30 USPQ2d 1481, 1483, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence.

Finally, University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404, 1405 held that:

...To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." *Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966(1997); In re Gosteli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989)* ("[T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed.") Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." *Lockwood, 107 F.3d at 1572, 41 USPQ2d at 1966.*

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 12-15 and 24-27 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Regarding claims 14-15, the claims recite "other tolperisone analogs" or "another tolperisone analog". It is not clear what "other tolperisone analogs" or "another tolperisone analog" refers to. The specification does not define the term and leaves the reader in doubt as to the meaning of the invention to which they refer, thereby rendering the definition of the subject-matter of said claims unclear.

Furthermore, the term "other tolperisone analogs" or "another tolperisone analog" allows for the inclusion of eperisone and silperisone which are already recited in claims 14 and 15, such redundancy renders the definition of the subject matter of said claims unclear.

Apart from the above reasoning, Markush-type language recited claims 13, 14 and 28 is a closed-ended language to list specified alternatives of a group in a claim. Since "other tolperisone analogs" allows for inclusion of unlimited number of compounds having "tolperisone analogs" characteristic or property (that are known today and those that may be discovered in the future), the recitation of "other tolperisone analogs" as alternatively usable substances or members in claim renders the definition of the subject-matter of said claims unclear.

Regarding independent claim13 and dependent claims 14-16 and 25-30, the phrase "including human" renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention.

A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. See MPEP § 2173.05(c). Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required

feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949). In the present instance, claims 12 and 15 recite the broad recitation "a mammal", and the claim also recites "including a human" which is the narrower statement of the range/limitation.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

5. Claims 13, 15, 25-27 and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lobisch et al. (US 5162346) in view of Cai et al. (US 6281211), and further in view of the applicant's admitted prior art of the record (page 1, line 25 through page 4, line 3).

.

Lobisch teaches the use of flupirtine for the treatment of neuralgia (or neuropathic pain), wherein said compound is administered in various dosage forms including oral or parenteral forms (column 2, line 67; column 3, lines 9-18; column 6, lines 42-43; and claim 2).

Cai is being supplied as reference to demonstrate the routine knowledge in using Na+ channel blocker such as riluzole, lidocaine, propafenone and semicarbazone derivatives for the treatment neuropathic pain (see particularly "Related Background Art" in column 1, lines 18-56 and "Summary of Actions"; abstract).

Applicant's admitted prior art of records teaches the use of sodium channel inhibitor or tolperisone in normalizing or maintaining muscle tone (spasticity).

The teaching of Lobisch mainly differs from the claimed invention in the combinatorial use of sodium channel flupirtine and sodium channel blocker such as lidocaine, propafenone and riluzole for the treatment of neuralgia or neuropathic pain. To incorporate such teaching into the teaching of Lobisch would have been obvious in view of Cai who teaches the use of sodium channel blocker, such as riluzole, lidocaine and propafenone for the treatment of neuralgia or neuropathic pain.

Above references in combination make clear that flupirtine and sodium channel blocker such as lidocaine, propafenone and riluzole have been individually used for the treatment of neuropathic pain. It is obvious to combine two compositions each of which is taught by prior art to be useful for same purpose; idea of combining them flows logically from their having been individually taught in the prior art. The combination of active ingredient with the same character is merely the additive effect of each individual component. See In re Kerkhoven, 205 USPQ 1069 (CCPA 1980).

With respect to the determination of various dosage forms (e.g., orally, rectally, intravenously, transdermally, subcutaneously or intracutaneously) and the current administration regimen of two drugs (e.g., simultaneously, separately or consecutively), such determination of appropriate dosage forms and administration regiment for treatment involving each of the above mentioned formulations is routinely made by those of ordinary skill in the art and is within the ability of tasks routinely performed by them without undue experimentation, especially in light of drug delivery information provided in the prior art references.

With respect to "said neuralgia pain or neuropathic pain is accompanied by an increase in muscle tone" in claim 27, the prior art reference(s) does/do not specifically mention the feature of the presence of "an increase in muscle tone" in the prior method. However, one having ordinary skill in the art would have expected at the time of the invention was made that such feature of the instant invention would have been characteristic of the modified prior art method. Especially, considering the state of art knowledge at the time of the invention was made as evidenced by the applicant's admission, one having ordinary skill in the would have expected that the administration of the instant combination containing sodium channel inhibitor would

benefit the patient suffering from neuropathic pain accompanying with the increase in muscle tone (spasticity). Thus, one would have been motivated to combine these references and make the modification because they are drawn to same technical fields (constituted with same ingredients and share common utilities), and pertinent to the problem which applicant concerns about. MPEP 2141.01(a).

6. Claims 14, 16, 28 and 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lobisch et al. (US 5162346) in view of Cai et al. (US 6281211), and further in view of the applicant's admitted prior art of record (page 3, lines 11-23).

The modified teaching of Lobisch et al. (Lobisch in combination with Cai) includes all that is recited in the claims 14 and 15 except the use of "tolperisone, eperisone and silperisone". The admitted prior art of record teaches tolperisone as sodium channel blocker similar to lidocaine.

One having ordinary skill in the art would have expected that tolperisone would behave similar as to the known sodium channel blocker such as lidocaine and provide therapeutic utility in the treatment of neuropathic pain through sodium channel blocking mechanism. One would have been motivated to combine these references and make the modification because they are drawn to same technical fields (constituted with same ingredients and share common utilities), and pertinent to the problem which applicant concerns about. MPEP 2141.01 (a).

Response to Arguments

7. Applicant's arguments filed December 13, 2007 have been fully considered but they are not persuasive.

Applicant's argument in the response takes the position that potassium channel openers and sodium channel blockers are not equivalent substances and each are distinct art recognized classes of materials. Applicant alleges that one of ordinary skill in the art would not have arrived at the claimed invention since Cai implies that the use of sodium channel blockers to treat neuropathic pain is unusual.

This argument is not found persuasive. It is generally known in the art that neuropathic pain is difficult treat and that different classes of drugs are routinely combined and utilized to treat neuroapthic pain, for example EP1-type prostaglandin receptor antagonist in combination with NSAIDs or COX-2 inhibitors (see USP 6537991), NMDA receptor antagonist and α2 adrenergic receptor activator (USP 5925634), antiepileptic compound (e.g., a compound of formula II) in combination with analgesics, NMDA receptor antagonist or NSAIDS (USP 6451857), etc... Thus, one having ordinary skill in the art at the time of the invention was made would have expected that it is obvious to combine two compositions each of which is taught by prior art to be useful for same purpose; idea of combining them flows logically from their having been individually taught in the prior art.

Applicant's argument in the response takes the position that the unexpected results provided by the applicant in (Tables 1, 2, 3 and 4 which show that the measure muscle relaxation is significantly higher than that calculated assuming no synergy, ie.., efficacy is super-additive) is sufficient to rebut the examiner's rejection.

This argument is not found persuasive. Unlike the applicant's argument, there is no indication in the instant claims 13-16 and 25-30 that the synergistic muscle-relaxation effect or the reduction of undesirable effects of motor coordination must be essentially present in the claimed invention. In other words, the interpretation of the instant claims is not limited to the alleged unexpected results since the proffered evidence is not commensurate in scope with the claims. Thus, the examiner considers that the alleged results is insufficient to rebut the examiner's rejection and maintains the rejection of record.

In response to the applicant's argument that Tables 1-4 show the synergic effects associated with administration of combinations of flupertine and tolperisone, the examiner recognizes that the applicant only shows results of combination without showing each of the effects taken separately. Although the specification discloses that "the skeletal muscle relaxing effect of flupirtine is amplified superadditively by tolperisone, and vice versa", the examiner cannot properly determine whether the values recited in Tables 1-4 (either calculated or measured muscle relaxation percentage) is greater than each individual of flupirtine or tolperisone. Again, in absence of each effect of tolperisone and flupirtine, the examiner determines that the cited references in combination make obvious the instant invention.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge

generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992).

Conclusion

8. No claim is allowed.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Kwon whose telephone number is (571) 272-0581. The examiner can normally be reached Tuesday through Friday from 9:00 am to 7:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel, can be reached on (571) 272-0718. The fax number for this Group is (571) 273-8300.

Any inquiry of a general nature of relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications may be obtained from Private PAIR only. For more information about PAIR system, see http://pair-direct.uspto.gov Should you have any questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

/Brian-Yong S Kwon/
Primary Examiner, Art Unit 1614